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COMPLETE SPECIFICATION
DRAWINGS ATTACHED

Percutaneous Administration of Physiologically Active Agents

I, FRIEDRICH MEYER, of 20 Schönenfelder Strasse, Hamburg-Wilhelmsburg, Germany, a German Citizen, do hereby declare the invention for which I pray that a patent may be granted to me and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a composite unit for dispensing dose quantities of physiologically active material for percutaneous absorption.

The application of salves, ointments, liniments, powders, which may contain pastes, cerates, or other externally applicable preparations of physiologically active agents to the outer skin surface has been employed by the medical profession and in the cosmetic arts for a long time. This method of application may have for its purpose to bring about a topical effect, for instance, it may cause local disinfection or it may be intended for a far-reaching absorption effect extending also to other parts of the body than those where the preparation has been applied topically, such as, for instance, the long known treatment with a mercurial ointment, i.e. with unguentum hydrargyri, used in the treatment of syphilis.

There are numerous other examples of the topical application of medication for local effect but only comparatively few examples for systematic action. The reason for this is that it is quite easy topically to apply to the skin in this manner a definite quantity of a liquid, a powder, an ointment, a jelly, or the like preparation. Yet in most cases it is not possible to determine how much of the medication has been taken up by the organism through absorption or whether it only superficially penertated the skin. Furthermore, it is also usually not possible to determine how much of the preparation has evaporated or how much of it remains on the skin as non-penetrating residue.

Up to the present time it was not possible to regulate and control the percutaneous absorption of a specific material, i.e. to cause a definite quantity of material (an exact dose) to be absorbed. Examples of uncontrolled percutaneous absorption have occurred with ointments containing salicylic acid, which ointments have even caused serious toxic effects and even death through poisoning. However, in few cases, percutaneous dispensing of relatively toxicologically harmless active agents has proven to be more or less effective, for instance, in the treatment with hormone preparations.

In general it can be stated that the lack of a method of percutaneously administering a precise dose of a therapeutically active agent to be absorbed by the skin had the result that percutaneous administration of such physiologically active agents found only limited use in medical practice. This is so, notwithstanding the pressing need for a method of administration of this type and for means for carrying out such a method. This need is evidenced by numerous publications concerning skin permeability. See, for instance, J. W. Hadgraft and G. F. Somers in "J. Pharm. Pharmacol". vol. 6, page 944 (1954); and J. W. Hadgraft, G. F. Somers, and H. S. Williams in "J. Pharm. Pharmacol". vol. 8, page 1027 (1956); as well as of Gemmell and Morrison in "J. Pharm. Pharmacol". vol. 9, page 641 (1957), two things clearly emerge from these publications:

1. The extensive protective and defence function of human skin toward outside chemical influences.

2. The extensive and practical interest in the percutaneous dispensing of therapeutically active agents. One condition of such percutaneous administration is, that a definite and as complete an absorption as possible as well as administration of the required dosage can be achieved.

It is one object of the present invention to provide a new and highly advantageous unit for percutaneously administering therapeutically and cosmetically effective agents.

It is another object of the present inven-

tion to provide a unit for dispensing definite doses of physiologically active agents by way of application to the skin for absorption of definite dose quantities by the skin.

The new process according to the present invention which will be described more in detail hereinafter and which permits the administration of therapeutically or cosmetically active agents through the skin, has made possible a number of substantial advantages:

1. Active agents, which normally are not absorbed by the skin or are only taken up sparingly, are now rendered readily absorbable.

2. The percutaneous absorption of active agents, which normally penetrate the skin only in small quantities, or only slowly from conventional preparations such as ointments, jellies, or solutions (for instance, containing salicylic acid, iodine, or hormones), is definitely promoted or accelerated.

3. Percutaneous absorption becomes readily controllable and can be adjusted so that it is practically complete.

4. Percutaneous absorption of the active agent can exactly be dosed.

These advantages permit in many cases percutaneous administration of active agents, which heretofore could be administered only parenterally. Both methods of administration can now be used equally well. It is, of course, understood that percutaneous application according to the present invention cannot replace all forms of parenteral administration, for instance, it cannot replace administration by intravenous injection when the introduction of the active agent by this route is necessary in order to cause rapid action of the active drug, likewise it cannot replace administration by injection into the cerebro-spinal fluid in the spinal canal.

The present invention shows the following advantages over the usual forms of injection, i.e. over subcutaneous, intracutaneous, intramuscular, and even over intravenous injections:

(a) Less annoyance for the patient since the pain of injection is absent;

(b) less danger of infection;

(c) more convenient handling for the physician, since sterilization of syringes and needles is dispensed with.

The present invention has the further particular advantage that it permits non-disturbing, convenient, and at the same time safe administration of such active agents which on oral adminstration are partially or totally destroyed in the gastro-intestinal tract, or which for other reasons are not absorbed quickly enough or completely enough. Such agents are, for instance, curare and other alkaloids, barbiturates, strophanthin and other cardio-active glycoides, convallatoxin, adrenalin, acetyl choline, procaine or agents which are badly tolerated on oral administration, such as saponin containing drug extracts.

The present invention makes it further possible to vary within wide limits the rate of absorption of active agents. Heretofore such variation in the rate of absorption could be achieved only by enteral administration through the gastro-intestinal tract or parenterally by way of injection.

According to one aspect of the present invention there is provided a process of producing a unit for administering measured doses of physiologically active agents by percutaneous absorption, which process comprises applying a dose quantity of said physiologically active agent to an obsorbent carrier layer, providing a non-absorbent, non-permeable separator layer superposed over said carrier layer, providing an absorbent reservoir layer superposed over said separator layer and providing wick means adapted to bypass said separator layer and to connect said carrier layer with said reservoir layer, the arrangement being such that upon applying the carrier layer together with said overlying layers to the skin, transporting liquid will flow from said reservoir layer to said carrier layer through the wick means, said physiologically active agent being dissolved by said transporting liquid and conveyed into the skin.

According to another aspect of the present invention there is provided a composite unit for the administration of measured doses of physiologically active agents for percutaneous absorption which unit comprises a carrier layer of absorbent material adapted to be impregnated with said active agent, a separator layer of non-absorbent, non-permeable material superposed over said carrier layer, a reservoir layer of absorbent material disposed above said separator layer and adapted to be filled with a transporting liquid, and wick means adapted to bypass said separator layer and to place said reservoir layer and said carrier layer in communication with each other.

The manner in which the process according to the present invention is carried out will become apparent from the following description and the accompanying drawings, in which

Figure 1 is a top plan view of a plaster-like device embodying the present invention;

Figure 2 is a cross-sectional view taken along line 2-2′ of Figure 1;

Figure 3 is a cross-sectional view of a modification of the embodiment illustrated in Figure 2;

Figure 4 is a cross-sectional view of another embodiment of the present invention; and

Figure 5 illustrates curves showing the anesthesising effect of a preparation accord-

ing to the present invention.

In accordance with the present invention an active agent, which is to be absorbed by the skin, is measured out (by volume or by weight) in solid form, for instance, 0.1 mg. of *g*- or *k*-strophanthin, or in liquid form, for instance, 0.04 cc. of an 0.25% alcoholic solution of *g*-strophanthin, and is applied to an absorbent carrier for the active agent, for instance, paper, cellulose, silk, linen, nylon, or other artificial fibre tissue, or like absorbent material. The carrier material impregnated with a measured predetermined amount of active agent may then be applied to the skin before or after completing the assembly of the parts of the preparation used in the present invention. This carrier material impregnated with active agent is then covered with a non-absorbent, non-permeable separator material having about the same surface area as the carrier material. The separator material may consist, for instance, of a film or foil of 0.1 mm. to 0.5 mm. thickness and made of rubber, wax paper, or a substantially liquid-impermeable synthetic resin, such as polyvinyl chloride. This separator material is preferably provided with one or more openings which have as their purpose to receive the wicks described more in detail hereinafter. Upon the non-permeable separator material there is placed the reservoir material. This reservoir material consists of a layer of absorbent fibrous material, such as cotton, paper, cellulose, linen, silk, nylon, or other natural or synethetic fibre material, and serves to take up the solvent, the function of which is also described hereinbelow. This reservoir has also about the same surface area as the carrier layer. However, it is thicker than the latter and has a thickness, for instance, of several mm. The reservoir has sufficient capacity to take up, for instance, from 0.5 cc. to 1 cc. of a suitable solvent or solvent mixture which is free of active agent. This solvent functions as a "guide rail" i.e., it causes the active agent to be absorbed by the skin by dissolving it out of the active agent carrier. The solvent and the active agent dissolved therein together penertate the skin. Therefore, the solvents are called "transporting substances" or "vehicles." The vehicle flows out of the reservoir carrier to the active agent carrier by means of one or more wicks which are made from absorbent materials, such as paper, wool, cotton, cellulose, silk, linen, nylon, or other synthetic fibres, and the like. The wick can be in the form of filaments, for instance, wool filaments, or in the form of bands, for instance, paper strips. These wicks connect the reservoir carrier with the active agent carrier. It is understood that the cross-sectional area of all the wicks together must be such that at least so much of the vehicle can flow therethrough (including the active agent dissolved therein) as will be absorbed by the skin from the active agent carrier. The aggregate cross-sectional area of the wicks will vary with the size of the skin surface area covered. Thus, for instance, if the carrier has an area of 40 sq. cm., the aggregate cross-sectonal area of the wicks will be larger than in the case where the carrier has a surface area of 4 sq. cm. The wicks can be conducted from the reservoir carrier to the active agent carrier either around the separator layer, in the case where no perforations are provided in said separator layer, or through small perforations in the separator layer.

Referring to Figure 2 of the drawings which is illustrative of the present invention, an adhesive layer is secured to the edges 1 of a covering 2 made of non-absorbent, substantially liquid and gas impermeable material which is flexible or non-fiexible, consisting, for instance, of synthetic plastic foil, such as polyvinyl chloride film, lacquer, rubber, glass, or other suitable materials. This cover 2 serves to prevent evaporation of the vehicle and/or to keep out the oxygen of the air, if readily oxidisable active agents and/or vehicles are employed. Disposed beneath the cover 2 is a reservoir carrier 6 which, as mentioned above, may be of cotton, paper, cellulose, silk, linen, nylon, or other synethetic fibre material. Located beneath the reservoir carrier 6 is a separator layer 3 which separates the reservoir carrier 6 from an active agent carrier 4. In this embodiment of Figure 2 of the separator layer 3 is not perforated and the active agent carrier 4 is in communication with the reservoir carrier 6 through a wick 5, which is drawn around the edge of separator layer 3. In this Figure, the carrier 4 may have an area of 4 sq. cm. and may be 0.2 mm. thick. The surface area of the other layers, such as of the reservoir layer 6 and the separator layer 3 are of substantially the same size. A protective strip 7 of any suitable material is provided to protect the carrier 4 from being soiled and to prevent evaporation of the solvent and/or active agent before use and on storage.

The various elements as shown in Figure 2 and described hereinafter, namely the active agent carrier 4, the separator layer 3, the reservoir carrier 6, the wicks 5, the cover 2, and the protective strip 7, are combined into a convenient unit or article of manufacture for carrying out the process according to the present invention. The size and the form of the various elements may be varied and adopted for various uses. For instance, in dispensing strophanthin, the normal dose of which is very small for humans and lies between 0.1 mg. to 0.2 mg., a carrier 4 having a small surface area of 4 sq. cm. is used. In this case wicks 5 of

paper strips 2 cm. wide are employed, which are conducted around the edges of the separator layer 3. A suitable reservoir carrier 6 is used which has an area of 4 sq. cm. and is 1 mm. to 2 mm. thick and made of a layer of cotton having a capacity of about 0.5 cc. to 1 cc. for the " transport substance " or vehicle.

In using the unit according to the present invention, a definite quantity of active agent or a solution thereof is placed on the carrier 4 which is preferably coloured to distinguish it from the other layers. The vehicle is then introduced in any suitable manner into the reservoir carrier 6 in the desired quantities according to the directions of use. The finally assembled unit of the various elements shown in Figure 2 is then placed on the skin and secured thereto by a bandage, a strip of adhesive tape, or the adhesive layer at 1. The assembly can also be made so that the carrier 4 is previously loaded with the necessary dose of active agent. In this case the user need only then apply the " transport substance " or vehicle to the reservoir carrier 6, for instance, by a pipette, either before or after the assembly is secured to the skin. The assembly can also be provided with means secured to it for fastening it to the skin, such as with an adhesive strip. In this case the carrier 4 and the active agent are protected from becoming dirty by a common protective layer 7 which is separated before use.

In the modification of this invention as shown in Figure 4 an arrangement is provided whereby a complete unit is supplied containing both the active agent carrier 4 impregnated with active agent and vehicle contained in the reservoir carrier 6. This arrangement is made possible through the use of a non-permeable confining or blocking layer 8 consisting, for instance, of a film of polyvinyl chloride or the like liquid-impermeable plastic material which serves to prevent putting into operation diffusion of the " transport substance " or vehicle through the wicks 5 into the active agent carrier 4 and dissolution of the active agent present in carrier 4.

In the use of this modification of the invention the assembled unit is placed on the skin and then blocking layer 8 is removed or torn, for instance, by pulling it out sideways. By this operation the wick 5 is brought into communication with reservoir 6 whereby the vehicle contained in the reservoir is conveyed to the carrier 4 and functions as described above.

The " transport substances " or vehicles that may be used in accordance with the present invention are liquids which must meet the following requirements:

1. They must be sufficiently absorbable through the unbroken skin.
2. They must have sufficient dissolving power for the active agent which is to be brought in contact with the skin for absorption.
3. They must be toxicologically unobjectionable for the skin or the whole organism.

The following " transport substances " or vehicles are particularly suitable for the purpose of the present invention:

(a) mono- or polyvalent primary, secondary, or tertiary aliphatic, cycloaliphatic, or aromatic alcohols containing 2 to 10 carbon atoms, such as hexanol, cyclohexanol, benzyl alcohol, butanediol-(1,2), glyceril; secondary or tertiary amyl alcohol, and 3-hexanol-1;

(b) aliphatic, cycloaliphatic, or aromatic hydrocarbons having 5 to 12 carbon atoms, such as *n*-hexane, *n*-hexane-(1), cyclohexane, and ethyl benezene;

(c) aliphatic, cycloaliphatic, or aromatic aldehydes, or ketones having 4 to 10 carbon atoms, such as heptyl aldehyde, cyclohexanone, and benzaldehyde;

(d) aliphatic, cycloaliphatic, or aromatic esters having 4 to 10 carbon atoms, such as amyl acetate, and benzyl propionate;

(e) ethereal oils or their aromatic constituents, such as oil of eucalyptus, oil of Rue, cumin oil, limonene, thymol, 1-pinen, carvone, and fenchone;

(f) halogenated aliphatic or cycloaliphatic hydrocarbons having 2 - 8 carbon atoms, such as *n*-hexyl chloride, *n*-hexyl bromide, and cyclohexyl chloride.

The low molecular compounds of this group, such as dibromoethane, trichloroethylene, are less suitable because of their low compatibility; however, they may be used in mixtures with other vehicles;

(g) mixtures of substances under (a) to (f) given above.

The following examples are further illustrative of the present invention. However, it is to be understood that this invention is not restricted thereto.

Example 1:

To an active agent carrier 4 of the unit illustrated in Figure 3, which consists of silk strips having a surface area of 2 sq. cm., there are applied 0.02 mg. of eserine base dissolved in 10.02 cc. of ethyl alcohol. The alcohol is then evaporated leaving carrier 4 uniformly impregnated with said eserine base. The active agent carrier is then covered with separator strip 3, consisting of a polyvinyl chloride film of 0.2 mm. thickness and having three perforations, one of them indicated at 9. On said separator strip 3 there is placed a resrevoir 6 consisting of a cellulose layer 3 mm. thick which is connected with carrier layer 4 by three wicks 5 (silk filaments 0.3 mm. thick) which pass through the perforations 9 in separator layer 3. The reservoir layer 6 is provided with

0.3 cc. of a vehicle mixture of amyl alcohol, *n*-hexanol, and cyclohexane in the proportion of 10:25:65.

The following pharmacological tests were carried out to show the advantageous effect of such a unit preparation in comparison with a conventional 1% eserine ointment:

Three of these assembled units are secured to shaved abdominal skin of 3 male mice having a body weight of from 18 g. to 20 g. with the aid of cover 2 and conventional adhesive tape strips 1. Within 30 minutes after application the known eserine effect on the striated muscles due to absorption of eserine is detected. There results an increase in chewing movement of periodic stimulation of the chewing musculature (masseter muscle) by constant, rectangular electric current impulses of 1/2 cycle per second, 2.5 m/sec. and 8 mA. Thirty minutes after the onset of the serine effect, the assembly is taken off and the non-absorbed residue on carrier 4 is determined according to the method described by F. Meyer and W. Schneider in "Arzneimittelforschung" vol. 1, page 165 (1951). Despite the sensitivity of this chemical analytical method, eserine is no longer detectable.

0.5 g. each of conventional eserine ointments containing 1% of eserine are applied to 4 sq. cm. of the shaved abdominal skin of two groups of 3 mice each. Lanoline ointment, i.e. an ointment consisting of one part of yellow petrolatum and one part of lanoline is used as ointment base for the first group of mice, while Unguentum cereum (German Pharmacopeia 6th edition), consisting of 7 parts of peanut oil and 3 parts of yellow wax is used as ointment base for the second group of mice. No eserine effect could be recorded with all six experimental animals on observation for 2 hours, although an amount of eserine is applied to the skin which is about 250 times as large as that applied by means of the assembled unit according to the present invention.

Example 2:

Three guinea pigs having a body weight of from 350 g. to 400 g. receive 1 mg. of *g*-trophanthin dissolved in 0.04 cc. of ethanol with the aid of a 4 sq. cm. carrier 4 made of filter paper which was affixed to their shaved abdominal skin, and the procedure was the same as described in example 1. The separator layer made of a film of polyvinyl chloride having an area of 4 sq. cm. and being 0.1 mm. thick was perforated in eight places 9 (Figure 3). Through these openings (0.3 mm. in diameter) 8 silk filaments 5 of 0.3 mm. thickness were pulled, said filaments 5 serving to form the wicks connecting reservoir 6 and carrier 4. A cellulose layer 0.5 cm. thick and having an area of 4 sq. cm. serves as reservoir 6. It is supplied and impregnated with 1 cc. of a vehicle liquid consisting of cyclohexanone, ethylene glycol, hexanol, and cyclohexane in the proportion of 10:10:50:30. The outside covering 2 is provided by a flexible polyvinyl chloride film having an area of 9 sq. cm. which is secured to the abdominal skin by means of a muslin bandage. All three animals show 30 to 45 minutes after application the typical poisoning effects of strophanthin, such as muscular tremor, convulsions, and respiratory impairment. The assembly is removed after 50 minutes. The non-absorbed residue on carrier 4 is determined with the aid of the colour reaction agent described by I. E. Bush and D. A. H. Taylor in "Biochem. J." vol 52, page 643 (1952). This reagent consists of 3.5 dinitro benzoic acid in alcoholic potassium hydroxide. The test results were only weakly positive as indicated by a slight rose colouration indicating the presence of traces of strophanthin, i.e. less than 0.005 mg. to 0.015 mg. approximately uniformly distributed over carrier 4. The same dose of 0.1 m.g. of *g*-strophanthin, and even a dose of 1 m. of strophanthin administered orally or, respectively, cutaneously in the form of an ointment has no noticeable effect.

Example 3:

Three guinea pigs having a body weight between 380 g. and 400 g. receive 0.1 mg. of *g*-strophathin by the aid of a unit preparation ready for use according to this invention. The unit is applied to the shaved abdominal skin of the animals. The active agent carrier 4 and the two wicks 5 (Figure 4) consist of filter paper strips 2 c.. wide and 6 c.m. long (Scheleicher & Schuell filter paper No. 2043 b). An area of 2 cm. by 2 cm. (4 sq. cm.) in the middle of these strips serves as active agent carrier 4. 0.1 mg. of *g*-strophanthin dissolved in 0.04 cc. of ethanol are applied to the carrier. Both ends of the strips (likewise 2 cm. x 2 cm.) serve as band forming wicks 5. They are passed around a separator strip 3 having an area of 4 sq. cm. and consisting of a non-perforated film of polyvinyl chloride having a thickness of 0.1 mm. as shown in Figure 4. A layer of pressed cotton 3 mm. thick and having an area of 4 sq. cm. serves as a reservoir carrier 6. Said layer is impregnated with 1 cc. of the "transporting liquid" or vehicle mentioned in example 2, i.e. with a mixture of cyclohexanone, ethylene glycol, hexanol, and cyclohexane in the proportion 10:10:50:30. The outside covering 2 consists of a flexible polyvinyl chloride film showing a surface area of 9 sq. cm. The edges 1 of said cover 2 are provided on their underside with an adhesive so that they form an adhesive tape which serves to secure the assembly to the skin. A blocking layer 8 of polyvinyl chloride is arranged between the reservoir 6 and the wick and carrier zone, and is secured at its margins to the outer covering

2, the blocking layer 8 being removed before using the unit so that the reservoir 6 communicates with the wicks 5.

Within 45 minutes after the application of such a unit to the skin of the three experimental animals there are observed in all the animals the poisoning effects described in example 2. Analysis of the residue in the carrier in accordance with the colour reaction method described above shows a difference from the results obtained in example 2. Non-absorbed residue is found only in the middle of the carrier in an ill defined band of about 2 mm. to 3 mm. width. This finding clearly demonstrates the functioning of the wicks, which are passed around the separator layer 3. They permit the vehicle liquid to flow into the carrier from the two sides, i.e. from the outer portion toward the centre.

Example 4:

Two groups each of three guinea pigs receive 0.1 mg. of *g*-strophanthin using a unit ready for use and applying said unit to the shaved abdominal skin of the animals. The same conditions as used in example 3 are employed. The only difference is that the vehicle liquid of examples 2 and 3 is replaced by the same volume of two different mixtures.

With the first group of three animals there is employed a mixture of cyclohexanone, ethylene glycol, *n*-hexanol, and cyclohexane as used in examples 2 and 3, but in other proportions, namely in the proportion of 5:15:70:10. With the second group of three animals a mixture of ethylene gycol and *n*-hexanol in the proportion of 70:30 is employed.

In cntrast to the results achieved with the vehicles of examples 2 and 3, wherein within 45 minutes after application of the unit according to the present invention the characteristic poisoning effects of strophanthin are observed, the results in these experiments are different. With the first group of animals (transporting liquid: cyclohexanone, ethylene glycol, *n*-hexanol, cyclohexane in the proportion 5:15:70:10) the above described toxic effects are observed only 3 hours after administration. With the second group of animals (transporting liquid: ethylene glycol and *n*-hexanol in the proportion of 70:30) the assembly is left on the skin for 20 hours without the slightest toxic effects being observed. After the expiration of such a period of observation of almost one day, the three units are removed and the amount of non-absorbed residue on the carrier is determined. Chemical analysis according to colour reaction method hereinbefore decribed, was negative. All of the active agent was absorbed (very slowly).

It is evident from these observations that the speed of percutaneous absorption of an active agent from an assembly according to the present invention can be varied within wide limits by varying the composition of the transporting liquid or vehicle.

Example 5:

For many purposes it is important to determine whether the quantity of therapeutically active agent applied has been completely taken up by the blood stream, i.e. to find out whether part of the active agent has been retained by the superficial skin layers. If this were the case, the active agent, for instance, the strophanthin, would also not have been detected in the residue on the carrier. The following experiments show that a measured quantity of *g*-strophanthin, administered according to the present invention, is quantitatively absorbed in the blood stream. As the small therapeutic doses of 0.1 mg. of strophanthin, as they are conventionally administered, cannot be detected with certainty by chemical anlysis in the blood, faeces, or the organs, biological methods must be used to find out how much of the strophanthin has entered the blood stream. In these experiments a predetermined quantity of *g*-strophanthin, such as one half of the lethal dose on intravenous infusion is applied to the skin. That this amount is quantitatively absorbed and has entered the blood stream can readily be ascertained by subsequently injecting intravenously the other half of the lethal dose. If all the animals are killed, it is obvious that all the strophanthin administered percutaneously must have been absorbed through the skin into the blood stream.

For this purpose fifteen guinea pigs (under urethane anaesthesia 2 g/kg. of body weight) were given by intravenous infusion lethal doses of *g*-strophanthin. The lethal dose amounts to 0.31 mg./kg. ± 0.048 mg./kg. at a speed of infusion of 0.0047 mg./min. To ten other animals similarly anaesthetised with urethane, there was administered half the lethal dose, i.e. 0.15 mg. of *g*-strophanthin per kg. body weight by means of a 4 sq. cm. carrier applied to the skin in accordance with the procedure of example 3. The assembly is allowed to remain on the skin for 90 minutes under the conditions of example 3, to cause absorption of the active agent. Thereafter it was determined which amount of strophanthin intravenously injected, causes death of the thus pretreated animals. It was found that 0.18 mg./kg. ± 0.08 mg. kg. are required to kill the aminals. Thus the sum of the amount of active agent absorbed percutaneously (0.15 mg./kg.) and that required to kill the animals on intravenous administration (0.18 mg./kg. ± 0.08 mg./kg.) corresponds approximately to the previously predetermined lethal dose of 0.31 mg./kg. Since the test with the residue on the 10 carriers according to the above described

colour reaction was negative, it has been proved that the quantity of active agent applied to the skin practically completey entered the blood stream. The present process not only permits absorption of toxic doses but also permits percutaneous absorption of exact, small, therapeutically effective doses.

In the same manner as described above in connection with *g*-strophanthin, other cardio-active glycoides, such as *k*-strophanthin and convallatoxine, various alkaloids such as morphine and strychnine as well as barbiturates, such as phenyl ethyl barbituric acid can be administered percutaneously in therapeutic as well as toxic does.

Example 6 :

Five guinea pigs receive 0.04 c.c. of a 10% solution of procaine in base form in *n*-hexanol with the aid of a 4 sq. cm. carrier 4 made of linen tissue. These carriers are applied to the shaved abdominal skin in the same manner as described in example 1. A separation layer 3 is placed over the carrier 4 also measuring 2 cm. × 2 cm. It consists of a flexible polyvinyl chloride film which is provided with 25 round openings of 0.2 mm. diameter. Silk filament wicks 5 are passed through each of these openings. The wicks 5 communicate with the superposed reservoir 6, which is made of a 3 mm. thick layer of cotton having a surface area of 4 sq. cm. The reservoir 6 contains 1 cc. of a transporting liquid or vehicle consisting of hexanol and cyclohexane in the proportion of 1 : 4. After allowing the unit to remain on the skin for 45 minutes, percutaneous absorption of the procaine is determined by its pain killing effect. Whether anaesthesia is achieved, is determined by exposing the animals to mechanical irritation or, respectively, to electrical irritation by means of rectangular electrical impulses of 30 cycles per sec. and a duration of 1 msec, with variations in current intensity of from 0.2 mA to 2.5 mA and determining the dose required to suppress pain reaction of the animal.

Example 7 :

Two volunteers are used in the following experiment. 1 mg. of procaine per sq. cm. of skin surface is applied to the untreated skin of the back of the left hand of each of the persons, under the conditions of example 6. After 40 minutes a very definite anaesthetic effect sets in. The intensity of electrical stimulation can be raised many times until reaction sets in. While the normal stimulus threshold is attained by the application of impulses of 0.2 mA. to 0.3 mA., percutaneous treatment with procaine according to the present invention raises said threshold to about 2 mA. before pain sets in. The unbroken curve in Figure 5, which illustrates the stimulus threshold in mA. plotted against time for various substances,, shows said anaesthesising effect which subsided only very slowly, i.e. within 60 minutes.

Example 8 :

The volunteers used in the experiment of example 7 receive, by application to the back of the hand, under the conditions described in examples 6 and 7, 1 mg. of procaine per sq. cm. of skin surface, and, in addition thereto, 1 mg. of 2—(a-naphthyl methyl) imidazoline nitrate. Said imidazoline compound was also present in the active agent carrier 4 containing the procaine base.

As shown in Figure 5, the anaesthetic effect produced by said mixture of procaine and imidazoline compound after an exposure of 40 minutes is somewhat greater (broken curve) than when procaine alone (unbroken curve) is applied. It follows that absorption of procaine by the deep layers of skin which are supplied with blood vessels can be retarded somewhat. Thus, it is possible to retain an active agent like procaine in the skin for a prolonged period of time or to attain a higher concentration of the active agent in the skin by the addition of the imidazoline compound, or as experiments have shown, a vasoconstrictor drug in general.

If, on the other hand, nicotinic acid amide or nicotinic acid methyl ester, each of which is a vasodilator, are added to the same dose of procaine, i.e. 1 mg. per sq. cm. of skin, the anaesthetic effect is reduced, as is evident from the dotted (lower) curve in Figure 5.

The results described hereinabove in the examples have been confirmed in actual clinical use, for instance, with cardiac patients to whom strophanthin was administered, with patients suffering, for instance, from intestinal distention or paresis to whom eserine was administered, with patients to be exposed to the action of local anaesthetics, such as procaine, with patients under morphine, for producing sedative and hypnotic effects, for instance, by administration of barbiturates, and others.

Of course, many changes and variations in the composition and size of the active agent carrier, the separator layer, the reservoir carrier, the blocking layer, the covering layer, the portective layer, and the adhesive, in the composition of the transporting liquid or vehicle, in the physiologically active agents, in the mode of impregnating the active agent carrier with the physiologically active agent and the reservoir carrier with the transporting liquid or vehicle, in the mode of applying and securing the asembled unit to the skin, and the like may be made by those skilled in the art.

WHAT I CLAIM IS:—

1. A process producing a unit for administering measured doses of physiologically active agents by percutaneous absorption,

which process comprises applying a dose quantity of said physiologically active agent to an absorbent carrier layer, providing a non-absorbent, non-permeable separator layer superposed over said carrier layer, providing an absorbent reservoir layer superposed over said separator layer and providing wick means adapted to bypass said separator layer and to connect said carrier layer with said reservoir layer the arrangement being such that upon applying the carrier layer together with said overlying layers to the skin, transporting liquid will to flow from said reservoir layer to said carrier layer through the wick means, said physiologically active agent being dissolved by said transporting liquid and conveyed into the skin.

2. The process according to Claim 1, wherein the transporting liquid is introduced into said reservoir layer from an outside source shortly before applying the layers to the skin.

3. The process according to Claim 1, wherein the reservoir layer is prefilled with transporting liquid and a removable blocking layer separating said reservoir layer from said wick means is provided.

4. The process according to Claim 1, wherein said transporting liquid comprises a solvent for said active agent, the solvent being selected from a group consisting of hydrocarbons, halogenated hydrocarbons, alcohols, aldehydes, ketones, carboxylic acid esters, said solvents having 2 to 12 carbon atoms, ethereal oils, the constituents of said ethereal oils, and mixtures of said solvents.

5. The process according to Claim 1, wherein the carrier layer is impregnated with a physiologically active agent and an agent affecting percutaneous absorption of said active agent.

6. A composite unit for the administration of measured doeses of physiologically active agents for percutaneous absorption which unit comprises a carrier layer of absorbent material adapted to be impregnated with said active agent, a separator layer of non-absorbent, non-permeable material superposed over said carrier layer, a reservoir layer of absorbent material disposed above said separtor layer and adapted to be filled with a transporting liquid, and wick means adapted to bypass said separator layer and to place said reservoir layer and said carrier layer in communication with each other.

7. A composite unit as claimed in Claim 6, and further comprising means for supplying a liquid to said reservoir layer.

8. A composite unit as claimed in Claim 6 or 7, wherein a non-permeable, non-absorbent blocking layer is provided between said reservoir layer and said separator layer to seaparte said layers from each other, said blocking layer, when in position, being adapted to prevent liquid from flowing from said reservoir layer to said carrier layer and adapted to be moved when the unit is to be used so as to bring said reservoir layer into contact with said underlying separator layer, and wherein the wick means are in contact with said carrier layer, and are adapted to be brought into communication with said reservoir when said blocking layer is moved.

9. A composite unit as claimed in any one of Claims 6 to 8, wherein said reservoir layer is charged with a transporting liquid for said active agent and wherein a cover layer is superposed over said reservoir layer and is adapted to prevent evaporation of said transporting liquid.

10. A composite unit as claimed in Claim 9, wherein the cover layer is provided at its borders with an adhesive layer adapted to secure the unit to the skin when in use.

11. A composite unit as claimed in any one of Claims 6 to 10, wherein a protective layer is provided adjacent to the carrier layer, said protective layer being adapted to be removed before use and application of said composite unit to the skin.

12. A composite unit as claimed in any one of Claims 6 to 11, wherein the separtor layer has perforations through which the wick means are passed to effect communication between the reservoir layer and the carrier layer.

13. A composite unit as claimed in any one of Claims 6 to 12, wherein the carrier layer and the reservoir layer consist of absorbent cotton, paper, cellulose, silk, linen or ysnthetic fibre material.

14. A composite unit as claimed in any one of Claims 6 to 11, wherein the separator layer, the lock layer, and the cover layer consist of non-absorbent non-permeable plastic material.

15. A composite package including in the composite unit claimed any one of Claims 6 to 14, and a source of said transporting liquid.

16. a composite package as claimed in Claim 15, wherein pipette means are provided for applying said transporting liquid to said reservoir layer.

17. A composite unit for the administration of measured doses of physiologically active agents for percutaneous absorption substantially as hereinbefore described with reference to the accompanying drawings, and/or the foregoing Examples.

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COMPLETE SPECIFICATION

This drawing is a reproduction of the Original on a reduced scale.

FIG.1

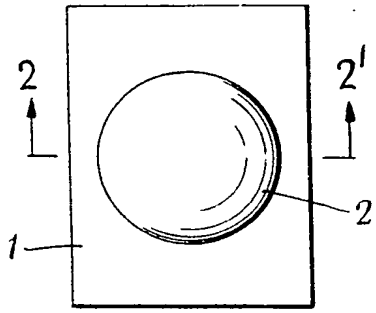

FIG.2

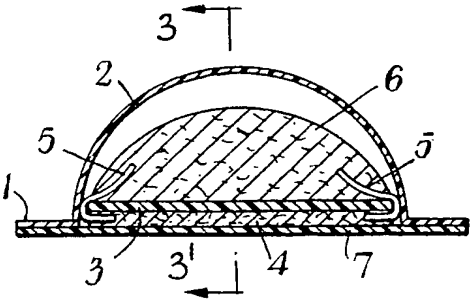

FIG.3

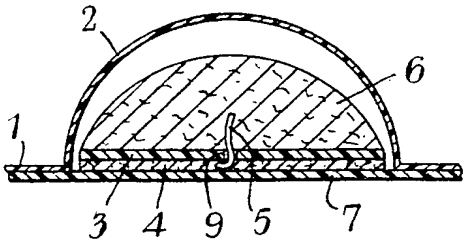

FIG.4

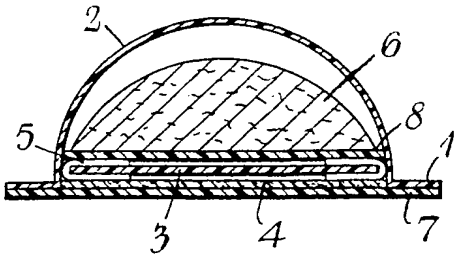

FIG.5